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(54) Title: TRANSGENIC NON-HUMAN ANIMALS CAPABLE OF PRODUCING HETEROLOGOUS ANTIBODIES

### (57) Abstract

The invention relates to transgenic non-human animals capable of producing heterologous antibodies, i.e., antibodies encoded by immunoglobulin heavy and light chain genes not normally found in the genome of that species of non-human animal. In one aspect of the invention, transgenes encoding unrearranged heterologous human immunoglobulin heavy and light chains are introduced into a non-human animal thereby forming a transgenic animal capable of producing antibodies encoded by human immunoglobulin genes. Such heterologous human antibodies are produced in B-cells which are thereafter immortalized, e.g., by fusing with an immortalizing cell line such as a myeloma or by manipulating such B-cells by other techniques to perpetuate a cell line capable of producing a monoclonal heterologous antibody. The invention also relates to heavy and light chain immunoglobulin transgenes for making such transgenic non-human animals as well as methods and vectors for disrupting endogenous immunoglobulin loci in the transgenic animal. The invention also includes methods to generate a synthetic immunoglobulin variable region gene segment repertoire used in transgene construction and methods to induce heterologous antibody production using animals containing heterologous rearranged or unrearranged heavy and light chain immunoglobulin transgenes.

and provides no teaching on coupling such neural stem cells to an electrical interface. Contrary to allegations made by the Examiner, Weiss et al. at col. 22, lines 56-60 and at col. 23, lines 37-45, merely describes implantation of cells, not implantation of a biosensor that includes both cells and an electrical interface. Nor does the Weiss et al. patent disclose a biosensor (including cells and an electrical interface) that can monitor a chemical, physiological or pathophysiological function.

Applicant requests withdrawal of the rejection of claims 74-76 and 78-84 under 35 U.S.C. § 101.

### §102 Rejection of the Claims

Claims 74-76 and 78-84 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent 6,238,429 to Markowitz et al. The Examiner alleges that Markowitz discloses all elements of the present claims.

Claim 74 is now directed to an implantable physiological or pathophysiological biosensor comprising: in vitro or ex vivo modified stem cells coupled to an electrical interface and adapted to be electrically coupled to endogenous tissue or cells when implanted into a mammalian subject at a site distant from a natural site for a physiological or pathophysiological function of the subject, wherein the in vitro or ex vivo modified stem cells can monitor a chemical, physiological or pathophysiological variable associated with the physiological or pathophysiological function of the subject and can produce a coagulation factor, serotonin, a growth factor, a hormone, or a receptor.

Applicant submits that Markowitz is limited to biological cables that span the totality of the distance between two tissues. Markowitz discloses nothing about a biosensor "implanted into a mammalian subject at a site distant from a natural site for a physiological or pathophysiological function of the subject." Accordingly, the Markowitz reference is missing at least one element of the present claims.

In addition, Markowitz is limited to *biological* cables – cables made of cells and other biological materials. Markowitz discloses nothing relating to electrical interfaces. For example, while the Examiner points to Markowitz FIGs. 5 and 6 allegedly disclosing a "device" that includes a wire, wire leads, tub, tubing or electronic pacemaker, Markowitz is actually limited to

AMENDMENT AND RESPONSE UNDER 37 CFR § 1.111

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cables of cells coated with fibrinogen or fibers (see Markowitz at col. 3, lines 20-30, which describe FIGs. 5 and 6). Thus, *none* of the following terms appear anywhere in the Markowitz disclosure:

- 1) "electrical interface"
- 2) "wire"
- 3) "tube"
- 4) "tubing"
- 5) "electronic"
- 6) "coagulation"
- 7) "factor" (appearing only in the title of a reference citation)
- 8) "serotonin"
- 9) "growth factor" (appearing only in the title of a reference citation)
- 10) "hormone"
- 11) "receptor"

In addition, Markowitz does not disclose the use of cells that can produce a coagulation factor, serotonin, a growth factor, a hormone, or a receptor.

Accordingly, the Markowitz patent fails to disclose at least three elements of the present claims. First, Markowitz fails to disclose a biosensor "implanted into a mammalian subject at a site distant from a natural site for a physiological or pathophysiological function of the subject." Second, Markowitz fails to disclose an electrical interface as claimed by the present claims. Third, Markowitz fails to disclose the use of cells that can produce a coagulation factor, serotonin, a growth factor, a hormone, or a receptor.

Applicant requests withdrawal of the rejection of claims 74-76 and 78-84 under 35 U.S.C. § 102(b).

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# **CONCLUSION**

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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